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Antiepileptic Drug Development: I. History and a Program for Progress

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INTRODUCTION

For many patients with epilepsy, the development of a new antiepileptic drug offers the only hope of achieving control of their seizures. For those patients whose seizures are controlled by currently available therapy, a new drug may reduce the toxic side effects they often tolerate to gain seizure control. Nevertheless, only three new antiepileptic drugs have been marketed in the United States since 1960, and few pharmaceutical firms today are interested in antiepileptic drug development.

Experimental methods for testing the anticonvulsant activity of new chemical compounds have been available for nearly 100 years (Albertoni, 1882). All but two of the antiepileptic drugs currently marketed in the United States were identified as anticonvulsants through these methods.

In contrast to the ease with which anticonvulsants may be identified, the development of these compounds into marketable antiepileptic drugs is complicated by the corporate assessment of their commercial value. Influencing that assessment are such factors as the difficulty of demonstrating efficacy, the unpredictability and high incidence of side effects that occur with chronic administration, conflicting evaluations of the need for new therapy and of the portion of the market capturable by a new antiepileptic drug, and the environment that governs the relations between the pharmaceutical industry and the regulatory agency.

The purpose of this paper is to review the history of the antiepileptic drugs currently marketed in the U.S. and to describe a federal government program meant to affect favorably the pharmaceutical industry's participation in antiepileptic drug development. A companion paper describes a screening program of the National Institute of Neurological and Communicative Disorders and Stroke which has succeeded in identifying a number of potential antiepileptic drugs.

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HISTORY OF THE MARKETED ANTIEPILEPTIC DRUGS

Development Before 1937

During the mid 1800s, a number of inorganic salts of bromide were reported to produce good sedative effect and were accepted into medical practice. Sir Charles Locock, in 1857, aware that potassium bromide had been noted to cause impotence, used it to treat catamenial seizures. He reported its success to the Royal Medical and Chirurgical Society, introducing drug therapy for the epilepsies. This development led other physicians to administer bromides to their patients whose seizures were uncontrolled by other therapies. Bromide's ability to reduce the seizure frequency in many of these patients led to the establishment of its efficacy and its subsequent widespread replacement of nondrug therapy.

Over the ensuing 50 years and in the absence of other effective agents, bromides were administered to epileptic patients for long periods of their lives. Many patients tolerated this chronic exposure poorly; although severe skin eruptions and psychoses surfaced only after prolonged administration, they were common toxic phenomena.

Phenobarbital, a new synthetic sedative-hypnotic drug, was marketed by Winthrop in 1912. In that same year, Hauptmann (1912) reported a reduction in the frequency of seizures in an epileptic patient receiving phenobarbital; subsequent clinical experience substantiated the drug's antiepileptic efficacy. It proved to be more effective than the bromides and patients taking it did not suffer their overt toxicity. Consequently, phenobarbital supplanted the bromides as the major antiepileptic drug.

The barbituric acid molecule was easily modified in the synthetic chemist's laboratory, and it was possible to test its major pharmacological action, sedation, in animals. Thus, molecular modification produced many sedative barbiturates, nearly 50 of which were marketed in the first 35 years of this century. One of these, mephobarbital, demonstrated good antiepileptic activity when given to man (Blum, 1932; Weese, 1932) and was marketed in the United States in 1935. Controlled trials comparing its antiepileptic efficacy with phenobarbital's indicated that in some patients mephobarbital was more effective and produced less sedation than phenobarbital (Page, 1936; Millman, 1939).

In the absence of animal models in which to test anticonvulsant activity, the discovery of the antiepileptic effect of the bromides and, later, phenobarbital and mephobarbital was the result of keen observation on the part of clinicians who used them to treat epilepsy. The demonstration of their widespread efficacy occurred after they were marketed in the United States. The paucity of effective drugs for epilepsy and the widespread need favored investment in antiepileptic drugs by the pharmaceutical industry. Government regulation of the marketing of drugs required only that they be accurately labeled (Federal Food and Drugs Act, 1906). The discovery of effective agents in an environment of need and unencumbered marketing resulted in a major advance in available therapy at the outset of the modern drug era.

Phenytoin—Preclinical Identification of Anticonvulsant Activity

In 1882, Albertoni reported the production of experimental seizures in dogs by direct faradic stimulation of the motor cortex. He was among the first to use such a procedure to test chemicals for anticonvulsant activity. Although Albertoni successfully investigated the properties of the bromides, atropine and a cinchona alkaloid, anesthesia and surgery limited the usefulness of his canine seizure model for identifying potential anticonvulsant drugs.

The convulsant properties of a number of naturally occurring chemicals were explored beginning in the late 1880s. Pentylenetetrazol was synthesized in 1924 and

used in several laboratories to test drugs for anticonvulsant activity soon after the first report of its convulsant action (Hildebrandt, 1926). Although it supplanted most other chemical convulsants, its use for screening anticonvulsant chemicals was not yet standardized and was considered unreliable (Putnam and Merritt, 1937; Merritt and Brenner, 1946).

Reports of a new electroshock technique for producing experimental convulsions in the intact animal (Spiegel, 1937) and of a similar technique for testing chemicals for anticonvulsant activity (Putnam and Merritt, 1937; Merritt et al., 1938) opened the door for experimental evaluation of chemicals prior to their administration to man.

Merritt and Putnam (1945) used their experimental technique to test more than 700 compounds between 1936 and 1945. Among the first compounds tested was phenytoin (Putnam and Merritt, 1937), which proved to be among the most potent. Because toxicology studies showed phenytoin to be well tolerated by laboratory animals, it was subjected to clinical trials. Merritt and Putnam (1938) reported phenytoin's clinical efficacy in 1938, the same year in which it was marketed. The time that elapsed between the first report of phenytoin's anticonvulsant effect in the cat and its availability on the market slightly exceeded 1 year. The large number of epileptic patients for whom barbiturates or bromides were ineffective, their dramatic improvement when phenytoin was added to barbiturate therapy, and the absence of a sedative effect were factors in this rapid marketing. In addition, entry into the market was regulated only by the 1906 laws.

Merritt and Putnam's demonstration of the anticonvulsant action and antiepileptic efficacy of phenytoin was a keystone event, not only because it provided a successful therapy for many patients with uncontrolled epilepsy but also because of its effect on the process of drug study and development. The success of their testing program demonstrated that an experimental method could lead to the discovery of compounds that would have clinical efficacy. The method's reliability and quantitative capacity made it feasible to test a large number of new chemicals for anticonvulsant activity. Administration to man, a more costly, time-consuming, and risky procedure, could confidently be reserved for the most effective experimental compounds. Phenytoin's apparently specific anticonvulsant action made it a unique tool for investigating neurophysiological phenomena, particularly for study of the mechanisms of seizure production and prevention. Finally, the process through which phenytoin came to the market demonstrated that academic investigators could work successfully with the pharmaceutical industry and encouraged a relationship which flourished throughout the succeeding 20 years.

Development of an Antiepileptic Armamentarium, 1938–1960

Following the introduction of phenytoin, a number of pharmaceutical firms undertook to improve or alter its activity by molecular modification. Also, investigators in both industry and academia began to explore new methods of seizure provocation that might improve on those of Merritt and Putnam. The discoveries in the chemistry laboratory complemented those of the pharmacologist; new drugs revealed new aspects of anticonvulsant pharmacology and new pharmacology revealed new anticonvulsant drugs.

In 1944, Richards and Everett reported that trimethadione, a potent analgesic compound (Spielman, 1944), prevented threshold seizures induced in rodents with pentylenetetrazol, by then a standard test. Subsequently, the same authors demonstrated that these seizures were also prevented by phenobarbital, but not by phenytoin (Everett and Richards, 1944). In 1945, Goodman and colleagues confirmed these findings by reporting that trimethadione

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and, to a lesser extent, phenobarbital raised the threshold for electrically induced minor seizures, whereas phenytoin raised it minimally, if at all. Furthermore, their data showed that phenytoin and phenobarbital, but not trimethadione, modified the pattern of maximal electroshock seizures. These results demonstrated the different anticonvulsant actions of these drugs and a qualitative difference between threshold and maximal seizures.

The pertinence of these findings to the testing of drugs for potential use in the treatment of epilepsy was supported by two pieces of evidence. The widespread use of electroshock therapy for the treatment of mental disorders provided ample opportunity for the observation of artificially produced seizures in humans. Kalinowsky and Kennedy (1943) found the pattern of seizures after electroshock to be very similar to that of the experimental animal undergoing the same stimulus. They reported the induction of both "major" and "minor" seizures by pentylenetetrazol and electroshock and the ability of phenobarbital and phenytoin to increase the amount of voltage necessary to elicit a maximal seizure. Confirmed by others (Strauss and Landis, 1938), this work established the similar response of the rodent and human nervous system to a seizure-provoking stimulus.

In 1945, Lennox's treatise on the petit mal epilepsies provided the other piece of supporting evidence. He administered trimethadione to 50 epileptic patients suffering from "petit mal, myoclonic, or akinetic" seizures not controlled by other medication. He found that trimethadione decreased or stopped the petit mal attacks, but failed to control, or even exacerbated, the grand mal attacks in 10 patients in whom this seizure type predominated. This unique action of trimethadione was later confirmed by the report of a larger series (Davis and Lennox, 1947; Lennox, 1947). The contrasting effects of trimethadione and phenytoin provided the correlation between the action of drugs in seizure disorders of man and maximal and threshold experimental seizure models. Trimethadione was marketed in 1946 and quickly became the drug of choice for absence seizures.

Between 1945 and 1949, a number of studies further defined the pattern of experimental maximal seizures (Goodman et al., 1945; Toman et al., 1946). In 1949, Goodman and associates proposed that phenytoin's anticonvulsant effect was due not to threshold elevation but to modification of the normal brain's ability to respond to seizure discharge within a focus. The supporting evidence was that phenytoin did not raise the threshold for minimal seizures, but did modify the pattern of a normal maximal seizure. Thus, they drew a distinction between maximal and threshold seizures rather than the kind or extent of evocative stimulus (Goodman et al., 1953). Protection against some electroshock seizure tests formerly thought to be due to threshold elevation was now recognized as the result of inhibited seizure spread. This conclusion resolved discrepancies in data which arose when drugs were tested by different seizure-provoking stimuli and shored up the theory on the mechanisms of action of antiepileptic drugs based on the effects of threshold elevation and modification of seizure spread.

In this same era, a number of new electroconvulsive seizure threshold tests were devised to test anticonvulsant drugs (Goodman et al., 1945; Toman et al., 1952). Among these was a low frequency (6 Hz) electroshock test which produced seizures consisting of abnormal behavior, "stunning," and automatisms reported to resemble "psychomotor" attacks in man (Toman et al., 1952). Phenacemide, a new anticonvulsant, proved to be the most potent drug evaluated in this "psychomotor" seizure test (Toman et al., 1952). Its clinical effectiveness was recognized when Gibbs and co-workers (1949) reported that it "greatly

improved" 50% of patients with complex partial seizures. Phenacemide's superior clinical efficacy to other available agents (not supported by current data) corroborated the experimental findings and lent credence to the notion that test systems could be devised which would identify drugs active in specific clinical seizure types.

Nevertheless, testing of the clinically active anticonvulsant drugs in a variety of experimental models failed to produce either a single test in which all drugs were active or consistent correlations between the results in a single test and clinical specificity. Even the specificity of the low frequency electroshock test was refuted (Brown et al., 1953). However, the use of various test batteries did uncover profiles of anticonvulsant activity which, with exceptions, correlated well with clinical efficacy and specificity (Goodman et al., 1945; Swinyard, 1949). By 1949, Goodman had acknowledged the importance of antiepileptic drug toxicity by incorporating tests of minimal neurological deficit into the evaluation of candidate anticonvulsants. Most test batteries thereafter included measures of drug toxicity (Goodman et al., 1949; Swinyard, 1949; Toman et al., 1952).

In 1951, Chen and colleagues investigated the anticonvulsant activity of approximately 65 α-phenyl succinimides, utilizing an abbreviated version of the Swinyard test battery (Swinyard, 1949). Among the most potent antipentylenetetrazol compounds were phensuximide and methsuximide, both of which were later marketed (1953 and 1957, respectively) for the treatment of absence seizures. Subsequent clinical experience with phensuximide raised doubts about its efficacy, which recently have been substantiated and explained (Porter et al., 1977*b*). Experience with methsuximide, on the other hand, indicated that it was occasionally effective in both generalized tonic–clonic and complex partial seizures, as well as in absence.

A third succinimide, ethosuximide, was marketed for the treatment of absence seizures in 1960, after earlier reports of its clinical effectiveness in this seizure type (Zimmerman and Burgemeister, 1958). A comparison of ethosuximide with its previously marketed analogs revealed it to be nearly as potent an inhibitor of subcutaneous pentylenetetrazol seizures as methsuximide, but far less potent against maximal electroshock (Chen et al., 1963).

In this same period (1938–1960), two analogs of phenytoin (mephenytoin and ethotoin), two of phenobarbital (metharbital and primidone), and an analog of trimethadione (paramethadione) were marketed (Table 1). All had spectra of activity similar to their parent drugs and were marketed for similar uses. Current applications of these drugs have been reviewed elsewhere (Woodbury et al., 1972).

Three other drugs, phethenylate, benzchlorpropamide, and aminoglutethimide (Table 1), were also marketed for use in epilepsy during this period. Both phethenylate and benzchlorpropamide, however, were withdrawn from the market by 1960. Phethenylate was found to cause a high incidence of hepatic necrosis (Pryles et al., 1952), and animal chronic toxicity studies of benzchlorpropamide were unfavorable (Lederle Laboratories, *private communication*, 1978). Aminoglutethimide was withdrawn in 1966, after it was found to cause a high incidence of goiters (Federal Register, 1966*a*,*b*).

Throughout this period, even when the number of marketed antiepileptic drugs was rapidly growing, there continued to be a perception that there was a need for additional antiepileptic drugs. The failure of some patients with common seizure types and of most with rare seizure types to respond to available agents, as well as recognition of the drugs' toxic side effects, heightened this perception.

The experimental evidence that new drugs might be specific for selected clinical

TABLE 1. *Antiepileptic drugs marketed in the United States*

Year introduced	International nonproprietary name	U.S. trade name	Company
1912	phenobarbital	Luminal	Winthrop
1935	mephobarbital	Mebaral	Winthrop
1938	phenytoin	Dilantin	Parke-Davis
1946	trimethadione	Tridione	Abbott
1947	mephenytoin	Mesantoin	Sandoz
1949	paramethadione	Paradione	Abbott
1950	phethenylate[a]	Thiantoin	Lilly
1951	phenacemide	Phenurone	Abbott
1952	metharbital	Gemonil	Abbott
1952	benzchlorpropamide[b]	Hibicon	Lederle
1953	phensuximide	Milontin	Parke-Davis
1954	primidone	Mysoline	Ayerst
1957	methsuximide	Celontin	Parke-Davis
1957	ethotoin	Peganone	Abbott
1960	aminoglutethimide[c]	Elipten	Ciba
1960	ethosuximide	Zarontin	Parke-Davis
1968	diazepam[d]	Valium	Roche
1974	carbamazepine	Tegretol	Geigy
1975	clonazepam	Clonopin	Roche
1978	valproic acid	Depakene	Abbott

[a] Withdrawn, 1952.
[b] Withdrawn, 1955.
[c] Withdrawn, 1966.
[d] Approved by FDA as adjunct.

seizure types and the improved definition of clinical seizures suggested that there might be a portion of the antiepileptic drug market which a new drug could capture exclusively. Furthermore, as long as the market experience of available drugs was limited, it was possible that new drugs might compete favorably for the same market. The uncertainty about side effects and the lack of extensive and comparative efficacy trials, even among available drugs, made the assessment of a drug's potential market difficult. But when only a few drugs were available for a given seizure type, and when none of those controlled the seizures of more than 70% of the patients, there remained the possibility that a new drug could complement available therapy sufficiently well to gain a place in the market.

The marketing of all drugs after 1938 was regulated by the Federal Food, Drug, and Cosmetic Act of 1938; it added to the 1906 labeling provisions the demonstration of safety as a prerequisite for marketing approval. Definitive questions about efficacy were usually not resolved until after a new drug was available for general use.

The cost of developing these new antiepileptic drugs was increased in comparison to the barbiturates and phenytoin. Major factors in the rising cost of development were the required safety studies and increasing competition, which demanded more assurance of success and hence more study and more investment prior to the marketing of a new drug. Nevertheless, 13 antiepileptic drugs were marketed in the United States between 1938 and 1960, suggesting that this cost was not considered extraordinary and unrecoverable. That attitude allowed the development of a drug armamentarium for the treatment of epilepsy that brought seizure control to many patients.

Decline in Development of Antiepileptic Drugs, 1955–1970

The unquestionable improvement that accrued to many epileptic patients from the

increased availability of effective antiepileptic drugs convinced the drug industry and many clinicians that the marketed drugs were adequate for the successful therapy of the epilepsies. The most effective methods of prescribing these drugs, their appropriate application to specific seizure disorders, and the optimum drug combinations to achieve maximum seizure control were yet to be found. The belief that better utilization of existing drugs was likely to lead to even further improvement in therapy helped to strengthen the impression that there was not a substantial need for new drugs.

Furthermore, the attention of the pharmaceutical industry had shifted to other areas of central nervous system (CNS) therapy. The discovery of tranquilizers and sedative-hypnotics, which achieved remarkable financial success, resulted in the expansion of CNS research into areas of pharmacology removed from anticonvulsants. In addition, the number of effective marketed antiepileptic drugs made it unlikely, in the view of the pharmaceutical industry, that a new drug could capture a sufficient market to justify the cost of its development. That cost, both in terms of money and scientific expertise, had been dramatically altered by the passage of the Drug Amendments Act of 1962 to the Federal Food, Drug, and Cosmetic Act (1938). It was these Kefauver–Harris amendments that first required the establishment of a drug's efficacy as a prerequisite for marketing approval.

Proof of the efficacy of a new drug in the treatment of epilepsy was seriously hampered by the lack of appropriate patient populations for controlled clinical trials. Patient populations with uncontrolled seizures, whose seizure types and frequency were well defined, were almost nonexistent. Many patients were reluctant to try experimental drugs and refused to participate in such trials. Either dramatic improvement or increased seizures caused others to withdraw from controlled studies.

The multiple drug therapy employed in the treatment of patients with uncontrolled seizures complicated the design of controlled trials that would establish the efficacy of a new drug alone. The differing response to medication of different seizure types required that a controlled trial demonstrate the efficacy of a new drug in defined seizure types. The definition of many of these seizure types remained controversial, and there were few patients whose seizures were confined to a single type. Furthermore, there was no rigorous methodology for the measurement of clinical response, and the medical and ethical guidelines for accepting patients for study were not developed (Cereghino and Penry, 1972). These factors combined to make it difficult to comply with the new regulations for marketing approval.

A survey of pharmaceutical firms conducted by the Epilepsy Branch for the U.S. Surgeon General's Public Health Service Advisory Committee on the Epilepsies (1967) revealed that many firms had no new antiepileptic drugs under development for marketing and that several of their drugs had not gained new drug approval because of inadequate proof of efficacy. A number of companies reported that they had discontinued the screening of new compounds for anticonvulsant activity, and others were known to have a significant number of anticonvulsant compounds whose development was not being pursued. The single most frequent reason cited for these developments was financial: the cost of development was prohibitive when compared to the expected return from marketing. Furthermore, an informal survey of academic medicinal chemists revealed that those who were synthesizing potential anticonvulsant agents had no ready access to appropriate pharmacological screening. Consequently, most had been forced to assign anticonvulsant synthesis a low priority.

The effect of these developments was a decline in the number of drugs being inves-

tigated as potential antiepileptics, and in the 12-year period of 1961 to 1973, no new drug was marketed in the United States with the control of epilepsy as the primary indication (Table 1).

STATUS OF ANTIEPILEPTIC DRUG THERAPY IN 1970

In 1970, it had been 10 years since the last new drug had been marketed for epilepsy, and the armamentarium now consisted of 13 drugs. The chronic administration of these had revealed numerous toxic effects that often complicated their use. In addition, a survey of the literature disclosed few acceptable controlled clinical trials of the marketed antiepileptic drugs (Coatsworth, 1971). Since all of the drugs had been marketed before the efficacy requirements of the Kefauver–Harris amendments of 1962, most claims of efficacy were based on retrospective studies, postmarketing uncontrolled trials, and case reports. There was no evidence that the efficacy of these drugs was as good as then perceived by clinicians or as it had appeared to be a decade earlier at the end of the era of rapid addition to the armamentarium.

The experience of the decade preceding 1970 had revealed shortcomings in both the efficacy and safety of available antiepileptic drugs. Some types of seizures still failed to respond to the available drugs. In these cases, neither the individual drugs nor drug combinations brought satisfactory seizure control, and it was clear that many patients could benefit from new drugs. Poor definition of some seizure types and improper diagnosis of others, even with well-defined criteria, further complicated therapeutic efforts.

In addition, common seizure types in a significant number of patients were not controlled on the existing drugs. Inaccurate diagnosis of seizure disorders sometimes resulted in the choice of inappropriate agents, and when proper agents had been selected, they were not always optimally administered. The methods for adequate control of antiepileptic drug therapy were neither well developed nor well disseminated.

Many patients whose seizures were controlled on existing therapy achieved seizure-free periods only at the expense of significant chronic toxicity. In many cases, the toxicity was subtle and appeared only after years of administration. The toxicity encompassed not only the CNS but connective tissue, bone, the hematopoietic system, and a variety of other systems. The pattern of toxic response to one drug could not be used to predict the response to others. The "sedative" side effect of a number of antiepileptic drugs emerged as an undesirable property of this class of drugs, especially in their long-term use. The prevalence of these toxic effects suggested that new, effective drugs with less toxicity would substantially improve the therapy of epilepsy.

These inadequacies of drug therapy suggested that attention to the definition and diagnosis of seizure disorders would lead to more rational selection of therapeutic agents and consequently to an increase in the number of patients whose seizures could be controlled. In 1966, the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke began to cooperate in a continuing international effort to improve and validate the classification of seizures and seizure disorders (Gastaut, 1970). It was also evident that the application of modern pharmacology to the use of currently marketed drugs would result in improved seizure control for some patients. The Epilepsy Branch has attempted to improve the methodology for quantitative analysis of blood levels of antiepileptic drugs and to extend the accurate use of blood drug levels into therapeutic practice (Rose et al., 1971; Kupferberg, 1972; Kutt and Penry, 1974; Kupferberg and Penry, 1975; Pippenger et al., 1976; Pippenger et al., 1978).

For many patients, however, it was clear that there was a definite need for new drugs.

DEVELOPMENT OF NEW ANTIEPILEPTIC DRUGS

Ongoing review of the status of therapy for epilepsy has led the Epilepsy Advisory Committee of the National Institutes of Health to conclude that improvements might come from drugs of equal efficacy but less toxicity than those currently available or from drugs of greater efficacy. In order to reach the market in 1970, new antiepileptic drugs satisfying these criteria had to undergo the development outlined in Fig. 1. Believing that this development process was a major factor in the lack of new drugs, the Advisory Committee recommended that the Epilepsy Branch begin to explore ways in which it might expedite antiepileptic drug development.

Since 1966, the Epilepsy Branch has attempted in three ways to effect a favorable change in the assessment of the market value of new antiepileptic drugs. Efforts have been made to demonstrate the need for new therapy, to bring an economy to the development of new drugs, and to demonstrate that there is a capturable market for a new antiepileptic drug, especially if it is more specific and less toxic than current therapy.

To demonstrate the need for new antiepileptic drugs, the Branch has supported epidemiological studies on the prevalence of various seizure disorders (Alter and Hauser, 1972; Rose et al., 1973; Cereghino, 1974). It has supported a compendium of

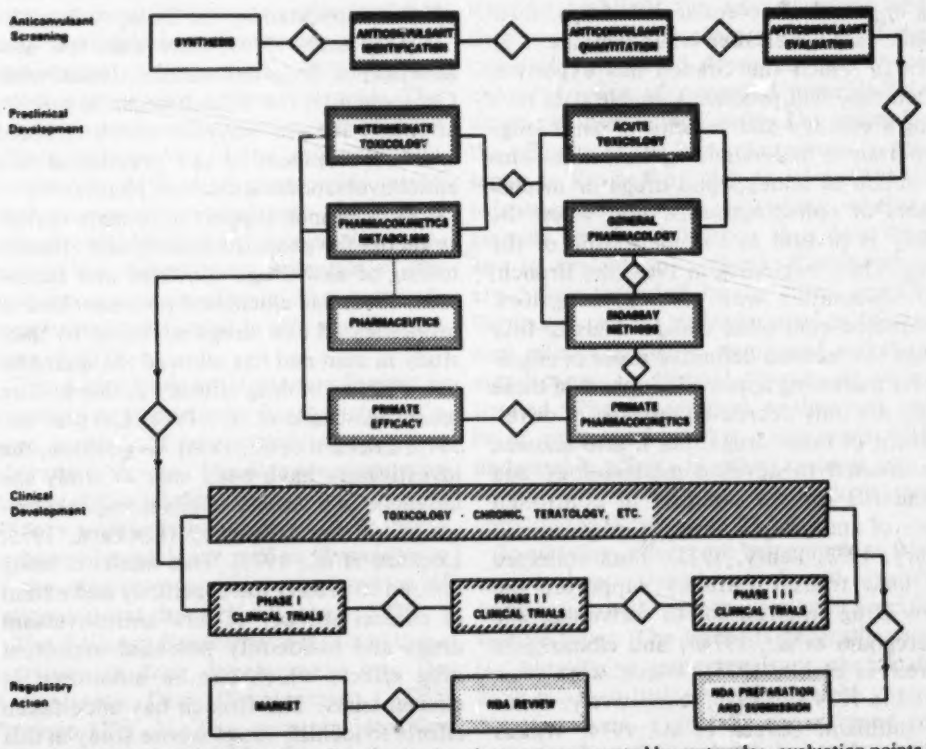

FIG. 1. Schema of the ADD Program. Development projects are represented by rectangles, evaluation points by diamonds. The development process proceeds from synthesis (*top*) to market (*bottom*).

the pharmacology and toxicology of currently available drugs (Woodbury et al., 1972). It has explored the deficiencies in the therapy of complex partial seizures (Penry and Daly, 1975), of absence seizures (Browne et al., 1975), and of infantile spasms (Lacy and Penry, 1976). Furthermore, it has attempted to highlight the significance of chronic toxicity in antiepileptic drug therapy (Porter et al., 1977*a*). The Branch has also supported a survey of the literature on antiepileptic drug efficacy (Coatsworth, 1971), which sought to identify the shortcomings of effective drugs, seizure types not well controlled with current therapy, and aspects of drug toxicity that complicate the use of available drugs.

In order to reduce the cost of development, the Epilepsy Branch has supported or conducted studies necessary for marketing approval of potential new drugs. Such studies are undertaken when they are in an area in which the Branch has expertise, when they will produce valuable data on a drug's efficacy and toxicity or knowledge important to understanding the mechanisms of action of antiepileptic drugs or mechanisms of epileptogenesis, and when the study is pivotal to the marketing of the drug. Thus, beginning in 1968, the Branch, in collaboration with other investigators, conducted controlled clinical trials of four drugs that needed definitive proof of efficacy for marketing approval. Support of these trials not only decreased the cost of development of these drugs, but it also allowed the Branch to develop methodology and standards for the conduct of controlled trials of antiepileptic drugs (Cereghino and Penry, 1972; Penry, 1973). Data collected in these trials eventually supported the New Drug Applications of carbamazepine (Cereghino et al., 1974*b*) and clonazepam (Dreifuss et al., 1975), which were marketed in 1974 and 1975, respectively. Trials on sulthiame (Green et al., 1974; Wilkus and Green, 1974; Dodrill, 1975) and albutoin (Cereghino et al., 1972; Cereghino et al., 1974*a*) failed to support their efficacy, and these drugs have not been marketed in the United States.

In 1978, valproic acid (VPA) was marketed in the United States for the treatment of absence seizures. Although VPA was synthesized in 1881, its anticonvulsant activity remained unrecognized until its serendipitous discovery 82 years later (Meunier et al., 1963). Valproic acid's clinical antiepileptic activity was demonstrated in 1964, and it was marketed in France 3 years later. By 1973, widespread marketing in Europe and reports of its clinical efficacy prompted the Epilepsy Branch to encourage the licensing of VPA in the United States. In 1974, Abbott Laboratories negotiated a license and filed an Investigational New Drug Exemption to begin clinical trials. The New Drug Application filed in 1977 included data from a controlled clinical trial supported by the Epilepsy Branch.

By the early 1970s, there were few new antiepileptic drugs approaching clinical trial. Consequently, the Branch began to turn its attention toward ways in which it could spur development in the preclinical and anticonvulsant identification phases.

Under Branch support, a primate epilepsy model for pharmacokinetic and efficacy testing of new drugs (Lockard and Barensten, 1967) has elucidated pharmacokinetic properties of new drugs pertinent to their study in man and has allowed the quantitative analysis of drug efficacy in this seizure model (Lockard et al., 1974; Levy et al., 1975; Lockard et al., 1975). In addition, the investigators have been able to study the influence of a variety of physiological stimuli on seizure frequency (Lockard, 1975; Lockard et al., 1975). This model is being utilized to predict the specificity and extent of clinical efficacy of new anticonvulsant drugs and to identify potential important drug effects which can be monitored in clinical trials. The Branch has undertaken efforts to identify drugs whose study in this model would help define their antiepileptic potential.

In 1975, the Anticonvulsant Screening

Project of the Epilepsy Branch began evaluating new chemical compounds for anticonvulsant activity (Krall et al., 1978). This project was established to provide a testing resource for academic medicinal chemists interested in the synthesis of anticonvulsants and to confirm or identify the anticonvulsant activity of compounds from commercial sources that were not being developed. The goals are to bring new anticonvulsant chemicals into a sphere where their development into antiepileptic drugs might become more favorable and to extend existing methodology for drug screening so that it might be more predictive of clinical usefulness. As of December 31, 1977, the project had tested more than 1,780 compounds from academic sources and the pharmaceutical industry.

The project was designed as a series of three screens. The first (anticonvulsant identification) identifies compounds that have anticonvulsant activity; 29% of those tested were active anticonvulsants. The second screen (anticonvulsant quantitation) defines the potency of the anticonvulsant compounds; 21% of all compounds tested were potent anticonvulsants. The third screen (anticonvulsant evaluation) appraises the antiepileptic potential of the most active anticonvulsants; 13 compounds were being investigated in this phase at the close of 1977.

The Anticonvulsant Screening Project is providing an opportunity for the study of a large number of compounds in constant laboratory settings. The data are supporting studies of the relationship between clinical efficacy and anticonvulsant activity in experimental models, as well as investigation of the structure–activity relationships of anticonvulsant drugs (Krall, et al., 1978).

The Epilepsy Branch has organized these activities in drug development into the Antiepileptic Drug Development (ADD) Program (Fig. 1). This program identifies those areas in which the Branch has, or expects to have, ongoing projects. Decision points in the development path allow monitoring of ongoing projects and justification of proposed studies. The ADD Program is helping the Branch to channel its expertise and financial resources expeditiously and to review systematically the progress of its developmental activities related to any particular drug. It has allowed the Branch to estimate the extent to which it can contribute to the development of a new antiepileptic drug and to monitor the impact of that contribution (Fig. 2).

In order to capture an acceptable portion of the antiepileptic drug market, a new drug must have superior efficacy or less toxicity than established drugs treating the same seizure disorders, have efficacy in a seizure disorder that is currently without drug therapy, or in combination with established drugs have improved efficacy over single-drug therapy. The Epilepsy Branch has tried to highlight the advantageous and detrimental pharmacological effects of the currently marketed drugs so that these characteristics of potential antiepileptic drugs are investigated early. For example, the efficacy of the benzodiazepines in epilepsy is limited by the development of tolerance. Studies to determine whether animals develop tolerance to a new drug and to evaluate the effects of withdrawal are being included in the third screen. Similarly, central nervous system depressant effects are being monitored and their significance to clinical toxicity is being studied. Pharmacological evaluations are being performed so that compounds with undesirable effects in other systems (e.g., cardiac depression, diuresis, acidosis) are identified early.

In addition, efforts are being made to find experimental methods which will identify compounds with selective action in specific seizure types. The methods generally used for identifying anticonvulsant chemicals have changed little over the last 25 years. New methods, especially those based on emerging knowledge about the mechanisms of action of antiepileptic drugs and the chemistry of neurotransmitters, are likely

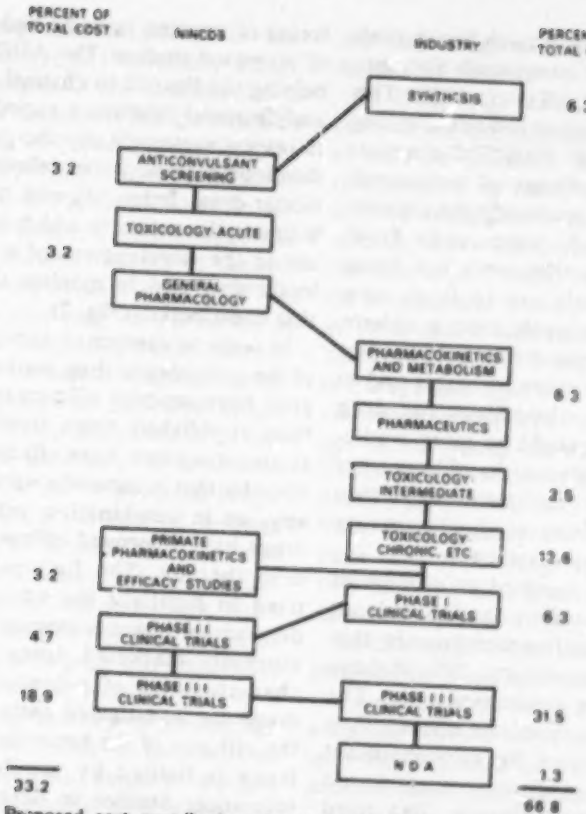

FIG. 2. Proposed cost contributions by the National Institute of Neurological and Communicative Disorders and Stroke and the pharmaceutical industry in the cooperative development of a new antiepileptic drug.

to yield drugs that are more selective in their action. Although not a formal part of the ADD Program, scientific investigation into such methods has been encouraged by the Branch. Its sponsorship of a symposium on laboratory evaluation of antiepileptic drugs in 1968 and a symposium on mechanisms of action of antiepileptic drugs in 1977, for example, fostered the exchange of information crucial to such developments. Better analyses of data derived from existing methods may also help to improve the prediction of antiepileptic efficacy of newly discovered anticonvulsant compounds (Krall, *in press*).

These approaches to antiepileptic drug development, namely substantiating the need for new therapy, reducing the cost of development, and seeking drug characteristics that will make them more specific, had attracted, by December 31, 1977, the participation of 32 pharmaceutical firms in the Anticonvulsant Screening Project, and five others had requested advice on drugs in preclinical development. At that time, four firms had 10 drugs in the anticonvulsant evaluation phase, three had one drug each in the preclinical development phase, and one had a drug undergoing clinical trial.

Additionally, the availability of a testing facility to evaluate compounds for anticonvulsant activity, together with a program designed to develop the market potential of active agents, has renewed the interest of

academicians in the synthesis and pharmacology of anticonvulsant drugs. Despite a shortage of research funds, more than 43 academic medicinal chemists had submitted nearly 800 compounds by the end of 1977. The antiepileptic potential of three of those compounds is now being studied.

CONCLUSION

In spite of the virtually unquestioned need for new therapy, the assessment of the commercial value of a new antiepileptic drug is likely to be unfavorable today if its development were undertaken by a pharmaceutical firm operating without support. Over the last 10 years, the Epilepsy Branch has attempted to contribute the scientific expertise and financial support necessary to effect a change in that assessment. The Antiepileptic Drug Development Program has not only helped to bring the three newest antiepileptic drugs to the market, it has effected a renewed interest in epilepsy and the drugs used to treat it.

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RÉSUMÉ

Malgré les besoins indiscutables en matière de thérapies nouvelles, l'évaluation de la valeur commerciale d'un nouveau médicament antiépileptique risque d'être défavorisée aujourd'hui si elle est entreprise par une firme pharmaceutique dépourvue de moyens suffisants. Au cours des 10 dernières années, l'Epilepsy Branch (du programme des maladies neurologiques des Instituts Nationaux de la Santé aux U.S.A.) a essayé de contribuer aux expertises scientifiques et aux subventions financières concernant cette évaluation. Le programme pour le développement des médicaments antiépileptiques de l'Epilepsy Branch a, non seulement aidé à commercialiser les trois médicaments antiépileptiques les plus nouveaux, mais il a provoqué un renouvellement d'intérêt sur l'épilepsie et les médicaments qui la traitent.

(J.-L. Gastaut, *Marseilles*)

RESUMEN

A pesar de la indudable necesidad de terapeúticas nuevas, es muy probable que la estimación del valor comercial de una nueva droga antiepiléptica no fuera favorable si su desarrollo se llevara a cabo por firmas farmaceúticas que operan sin un soporte complementario. Durante los últimos 10 años, la Epilepsy Branch ha intentado contribuir con los necesarios soporte económico y experiencia científica, para alterar la afirmación previa. El Programa de Desarrolo de Drogas Antiepilépticas ha servido no solo para presentar en el mercado las tres drogas antiepilépticas más recientes sino también para renovar el interés en la epilepsía y en las drogas que la tratan.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

Trotz der eigentlich unbezweifelten Notwendigkeit, neue Therapiemöglichkeiten zu finden, wirkt sich die Feststellung des kommerziellen Wertes neuer Antiepileptica heutzutage wahrscheinlich dann ungünstig aus, wenn die Entwicklung von einer pharmazeutischen Firma alleine ohne Unterstützung vorgenommen wird. Während der letzten 10 Jahre hat die Sektion Epilepsie versucht, wissenschaftliche Gutachten und finanzielle Unterstützung beizusteuern, um eine Änderung dieser Sachlage herbeizuführen. Das Programm zur Entwicklung antiepileptischer Medikamente hat nicht nur dazu beigetragen, die 3 neuesten Antiepileptica auf den Markt zu bringen sondern es hat auch zu einem neuerlichen Interesse an der Epilepsie und an den Medikamenten geführt, die zu ihrer Behandlung notwendig sind.

(D. Scheffner, *Heidelberg*)

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